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Post Hoc Analysis of the Phase II/III APRIL-SLE Study

Association Between Response to Atacicept and Serum Biomarkers Including BLyS and APRIL

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Objective. **To assess the relationship between treatment response, baseline biomarker levels, and atacicept exposure in patients with systemic lupus erythematosus (SLE) in the phase II/III APRIL-SLE study.**

Methods. **We performed a post hoc analysis of patients who received placebo, atacicept 75 mg, or atacicept 150 mg in a randomized, controlled, 52-week trial. Serum levels of BlyS and APRIL were measured at baseline, and serum levels of Ig and the numbers of naive B cells and plasma cells were measured at baseline and during treatment. Atacicept exposure was determined by assessment of the serum trough concentrations throughout the 52-week trial period. Associations between these parameters, treatment response (reduction in British Isles Lupus Assessment Group A or B flare), and infection rates were explored.**

Results. **Recurrent high baseline levels of both BLyS (≥1.6 ng/ml) and APRIL (≥2.2 ng/ml) correlated with a greater treatment response (flare rate 75.7% with placebo, and 50.0% and 32.0% with atacicept 75 mg and atacicept 150 mg, respectively) compared with lower baseline levels of both. Increased atacicept exposure correlated with reduced flare rates (60.5% with placebo; 63.4%, 61.0%, 48.8%, and 29.3% in the 4 quartiles, from lowest to highest atacicept exposure). Greater pharmacodynamic responses (reduced Ig levels and naive B cell and plasma cell numbers) were associated with greater reductions in the flare rate. Infection rates were similar regardless of biomarker levels at baseline or at the time of atacicept exposure.**

Conclusion. **These post hoc analyses demonstrate a dose-response relationship between atacicept concentrations, reduced Ig levels, and reduced flare rates and suggest that baseline biomarkers such as elevated serum levels of BLyS and APRIL may help to identify the patients who are most likely to benefit from atacicept treatment.**

Systemic lupus erythematosus (SLE) is a chronic, potentially fatal autoimmune disease characterized by unpredictable exacerbations and remissions, with protean clinical manifestations (1–4). The severity of disease ranges from mild to life-threatening, and many SLE patients consider their general quality of life to be poor (5,6). Patients with SLE are chronically exposed to drugs that have significant side effects, such as corticosteroids and immunosuppressive agents (7). There is a high unmet need for novel therapies with improved risk/benefit ratios that specifically target manifestations of SLE and improve patients' quality of life. New therapies

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should reduce the need for immunosuppressive agents and corticosteroids, control end-organ damage, reduce mortality, and limit side effects (8).

B cell abnormalities contribute to the clinical manifestations of SLE; therefore, diverse strategies have been proposed to target B cells in this disease (9,10). Patients with SLE who do not respond to treatment with standard immunosuppressive agents are increasingly considered for targeted biologic treatments directed at B cell–activating factors, B cells and T cells, and cytokines. Blockade of B cells is of specific importance, because lupus autoantibodies play a key role in the pathophysiology of the disease (11). Inhibition of the B cell–stimulating factor BLyS (also known as BAFF) (12) with the monoclonal antibody belimumab was shown to be effective for the treatment of SLE and to have an acceptable safety profile (13).

Atacicept (previously referred to as TACI-Ig) is a recombinant fusion protein comprised of the extracellular domain of the TACI receptor joined to a human IgG1 Fc domain (14). Like belimumab, atacicept inhibits BLyS. Atacicept also targets APRIL (12,14), another B cell–stimulating factor that plays a critical role in SLE pathogenesis (15) and promotes the survival of long-lived plasma cells and plasmablasts (16,17), which are believed to contribute to the production of autoantibodies observed in SLE (18). Both BLyS and APRIL levels are elevated in patients with SLE (15,19,20), which suggests that blocking the activities of both BLyS and APRIL by atacicept may result in an effective approach to treatment. In contrast to inhibition of BLyS alone, simultaneous inhibition of APRIL has the potential added benefit of targeting long-lived plasma cells, thus reducing autoantibody production.

In a phase II/III randomized, double-blind, multicenter, placebo-controlled trial (APRIL-SLE; n = 461) (ClinicalTrials.gov identifier: NCT00624338), there was no difference in flare rates between atacicept 75 mg and placebo (odds ratio [OR] 1.15, $P = 0.543$). Due to 2 fatal infections among patients receiving atacicept 150 mg (1 of which was caused by acute respiratory failure secondary to possible leptospirosis, which is an extremely rare cause of death in SLE), this treatment arm was terminated before it was fully enrolled. However, analysis of patients treated at the higher atacicept dose suggested efficacy in the prevention of flare ($P = 0.002$) and increased time to first flare ($P = 0.009$) when compared with placebo (21).

We performed a post hoc analysis to examine the relationships between atacicept efficacy and safety outcomes and patient biomarkers (BLyS and APRIL levels, Ig levels, and naive B cell and plasma cell numbers) as well as drug exposure levels in the potential completer population of the APRIL-SLE study, which includes all patients who were randomized more than 52 weeks prior to termination of the atacicept 150-mg arm and were therefore not affected by this discontinuation.

PATIENTS AND METHODS

Trial design. Details of the trial design and methods have been described previously (21). The trial was conducted in accordance with the Declaration of Helsinki. The trial protocol and all substantial amendments were approved by the relevant institutional review boards or independent ethics committees, and all patients provided written informed consent. Briefly, exclusion criteria included active moderate-to-severe glomerulonephritis or severe central nervous system lupus. Adult patients with SLE who were antinuclear autoantibody positive (HEp-2 dilution ≥1:80 or anti–double-stranded DNA [anti-dsDNA] antibody level ≥30 IU/ml) and had active disease (≥1 British Isles Lupus Assessment Group [BILAG] score of A and/or B) (22) at screening were enrolled and treated initially with a tapering course of corticosteroids.

Patients achieving a BILAG score of C or D in all systems at week 10, without any new A or B scores by week 12 (n = 461) while receiving prednisone 7.5 mg/day in weeks 11 and 12, were randomized to receive subcutaneous injections of atacicept 75 mg or 150 mg or matching placebo (1:1:1 ratio). Treatment was administered twice weekly for 4 weeks and then once weekly for the remaining 48 weeks.

The primary outcome measure was the proportion of patients with at least 1 adjudicated BILAG A/B flare, as defined by the BILAG index, during the 52-week trial period (termed "flare rate") (21). Secondary end points included time to first flare and safety. Post hoc analyses were performed to assess the relationship between treatment response (reduction in the number of patients with a new flare) and biomarker levels (pre-dose BLyS at baseline, pre-dose APRIL at baseline, changes in IgG, IgM, naive B cell numbers, and plasma cell numbers from baseline to week 52 [or last value during treatment in case of missing week 52 data]), and atacicept exposure (average serum trough concentration). The association between infection rate and biomarkers or atacicept exposure was also analyzed.

Statistical analysis. All patients included in these analyses were those who had been randomized at least 52 weeks prior to the termination of the 150-mg treatment arm. This population is defined as the potential completer population on the basis that, barring any need for treatment discontinuation, these patients would have completed the planned 52-week treatment. By focusing on this patient population rather than the intent-to-treat (ITT) population, any potentially confounding influence due to early termination of the 150-mg treatment arm was avoided, and comparability in exposure between treatment groups was ensured.

For the BLyS and APRIL analysis, baseline (pre-dose) serum levels of BLyS and APRIL were obtained, and subgroups based on BLyS and APRIL levels were investigated to identify whether a subset of patients with an enhanced response to atacicept existed. For other biomarker analyses and atacicept exposure analyses, patient data were divided into quartiles.

The primary efficacy end point was the percent of patients with a new adjudicated BILAG A/B flare during the 52-week treatment period (flare rate), and premature

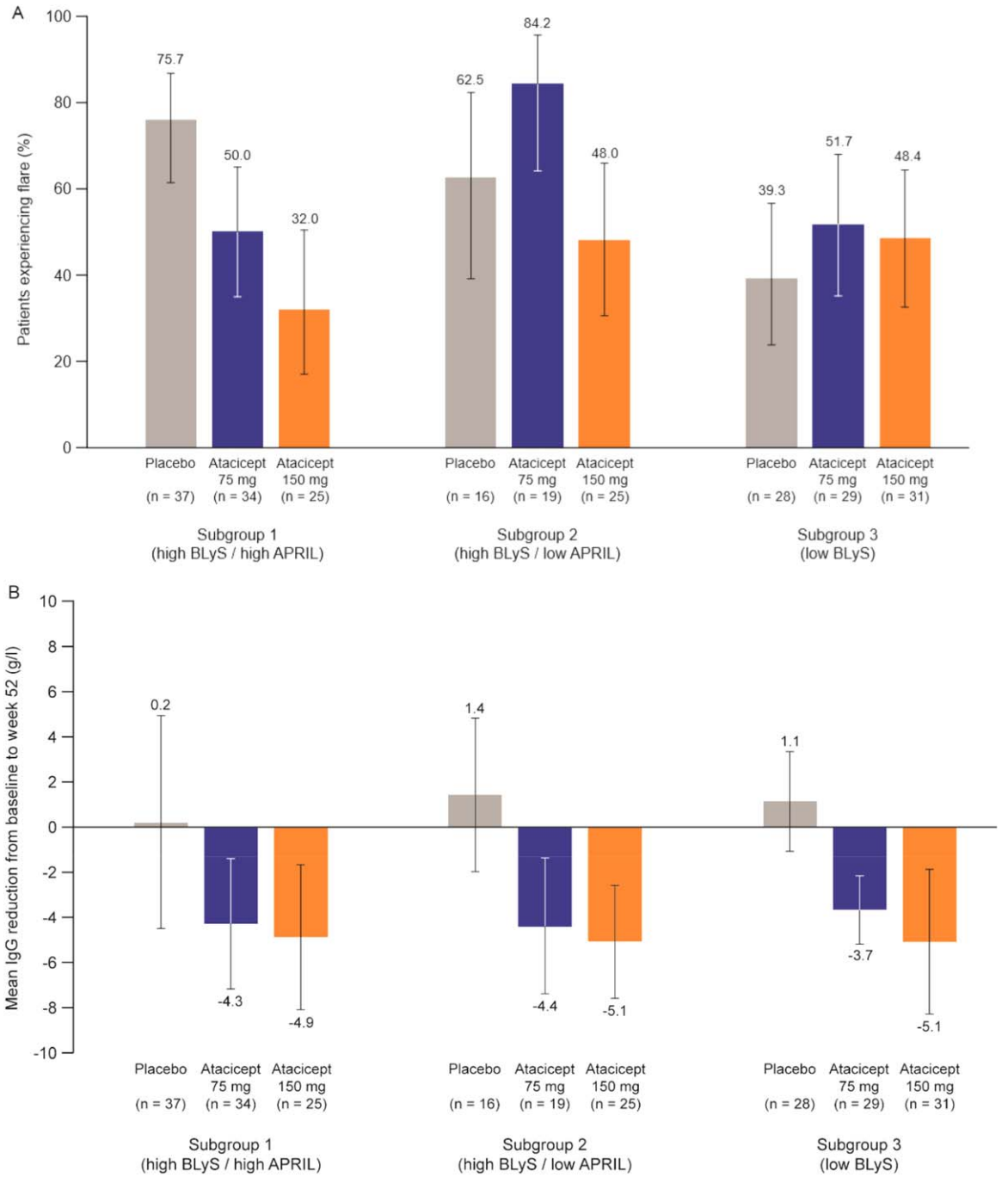

Figure 1. Atacicept treatment is associated with disease flare reduction in patients with high baseline serum levels of BLyS and APRIL (potential completer population). **A,** Flare rate (proportion of atacicept- and placebo-treated patients with a new flare) according to baseline levels of BLyS and APRIL. Lines represent the 90% confidence limit. **B,** Mean IgG reduction from baseline to week 52 in atacicept- and placebo-treated patients, according to baseline levels of BLyS and APRIL. The cutoff for high versus low BLyS levels was defined as ≥1.6 ng/ml. The cutoff for high versus low APRIL levels was defined as ≥2.2 ng/ml. Values are the mean ± SD.

discontinuation of study drug was imputed as new flare. Time to first new flare was estimated with Kaplan-Meier curves, and treatment discontinuation was handled by censoring.

RESULTS

Baseline characteristics. The demographic and baseline data were comparable across all treatment groups

in the ITT population. Among the 461 patients in the ITT population, 246 were included in the potential completer population: 81 in the placebo group, 84 in the atacicept 75 mg group, and 81 in the atacicept 150 mg group (21).

The baseline distributions of pre-dose BLyS and APRIL levels were similar between treatment groups. Median baseline BLyS levels were 1.9 ng/ml in all treatment groups. A total of 40% of samples were below the lower limit of quantification (LLQ) for the BLyS assay (1.56 ng/ml) and were imputed to be the LLQ value. Median baseline APRIL levels were 2.4 ng/ml, 2.3 ng/ml, and 2.2 ng/ml in the placebo, atacicept 75 mg, and atacicept 150 mg groups, respectively. No samples were below the LLQ of 0.3125 ng/ml for the APRIL assay. The baseline serum levels of Ig as well as the naive B cell and plasma cell counts were comparable between treatment groups.

Treatment response. *Identification of patient subgroups with different degrees of treatment response according to baseline BLyS and APRIL levels.* A marked difference in response to atacicept 150 mg (reduced rate of flares) was observed in patients with baseline BLyS levels of ≥1.6 ng/ml compared with those with baseline levels of <1.6 ng/ml (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39809/abstract). In the group with a BLyS level of ≥1.6 ng/ml, there was a trend toward a greater treatment response in patients with higher levels of APRIL (see Supplementary Tables 2 and 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39809/abstract). A subset of patients with baseline BLyS levels of ≥1.6 ng/ml and baseline APRIL levels of ≥2.2 ng/ml was identified as having a significant treatment response compared with placebo. A subset of patients with baseline BLyS levels of ≥1.6 ng/ml and baseline APRIL levels of <2.2 ng/ml was identified as having a moderate treatment response compared with placebo. In the remaining population of patients with BLyS levels of <1.6 ng/ml, no difference in treatment response based on APRIL levels was detected (data not shown). Therefore, 3 distinct BLyS/APRIL subgroups could be defined based on the response to atacicept: subgroup 1 (high BLyS/high APRIL), subgroup 2 (high BLyS/low APRIL), and subgroup 3 (low BLyS).

Relationship between treatment response and baseline BLyS and APRIL levels. In patients receiving placebo, flare rates were 75.7%, 62.5%, and 39.3% in BLyS/APRIL subgroups 1, 2, and 3, respectively. In subgroup 1, atacicept treatment at both doses was associated with a reduced flare rate compared with placebo; however, this effect was most pronounced with the higher dose of atacicept (75.7% in the placebo group, 50.0% in the atacicept 75 mg group, and 32.0% in the atacicept 150 mg group). In subgroup 2, the flare rate was reduced compared with placebo only at the highest atacicept dose (62.5% in the placebo group, 84.2% in the atacicept 75 mg group, and 48.0% in the atacicept 150 mg group). No reduction in the flare rate was observed with atacicept compared with placebo in subgroup 3 (39.3% in the placebo group, 51.7% in the atacicept 75 mg group, and 48.4% in the atacicept 150 mg group) (Figure 1A).

Examination of IgG levels in the BLyS/APRIL subgroups revealed a dose-dependent correlation between the mean IgG change from baseline to week 52 and atacicept treatment that was comparable in all 3 subgroups (Figure 1B). These results suggest that differences in response between subgroups were not solely attributable to the reductions in IgG levels.

Atacicept treatment appeared to delay the time to new flare in subgroup 1 (Kaplan-Meier 25th percentiles 85 days with placebo, 275 days with atacicept 75 mg, and at least 365 days with atacicept 150 mg [as the number of patients experiencing a new flare was not reached in the 25th percentile within 52 weeks]), but not in subgroups 2 and 3 (see Supplementary Table 4, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39809/abstract).

Relationship between treatment response and IgG, IgM, IgA, naive B cells, and plasma cells. To analyze the relationship between treatment response and a reduction at 52 weeks relative to baseline in IgG, IgM, and IgA levels, naive B cells, and plasma cells, data on atacicept-treated patients were divided into quartiles. In addition to reductions from baseline to 52 weeks, data on the lowest IgG values recorded during the treatment period were also divided into quartiles and analyzed.

In terms of IgG levels, atacicept treatment was associated with reduced flare rates compared with placebo in patients with the highest reduction in IgG levels relative to baseline (60.5% in the placebo group, 38.5% and 37.5% in the first and second quartiles, respectively, compared with 60.0% and 62.5% in the third and fourth quartiles, respectively) (Table 1), and in those who achieved the lowest IgG levels during the study period (43.6% and 34.1% in the first and second quartiles, respectively, compared with 61.1% and 60.0% in the third and fourth quartiles, respectively) (data not shown). Flare rates were also reduced with atacicept compared with placebo in patients with the greatest reductions from baseline in IgM levels (43.6%) and IgA levels (35.9%) (results not shown), as well as those with the greatest reductions in naive B cells and plasma cells (42.1% and 47.4%, respectively) (Table 1).

Table 1. New disease flares in placebo- and atacicept-treated patients in the potential completer population, according to IgG, naive B cell, and plasma cell changes from baseline to week 52*

	No. of patients	New flare during treatment
Placebo	80†	49 (60.5) [0.508–0.696]
Atacicept		
Change in IgG, gm/liter		
First quartile (−15.4 to −6.3)	39	15 (38.5) [0.254–0.529]
Second quartile (−6.2 to −4.0)	40	15 (37.5) [0.247–0.517]
Third quartile (−3.9 to −2.9)	40	24 (60.0) [0.458–0.731]
Fourth quartile (−2.8 to 2.0)	40	25 (62.5) [0.483–0.753]
Change in naive B cells/μl		
First quartile (−725.0 to −125.0)	19	8 (42.1) [0.230–0.632]
Second quartile (−124.0 to −44.0)	20	7 (35.0) [0.177–0.558]
Third quartile (−41.0 to −12.0)	18	11 (61.1) [0.392–0.801]
Fourth quartile (−11.0 to 39.0)	21	12 (57.1) [0.372–0.755]
Change in plasma cells/μl		
First quartile (−107.0 to −13.0)	19	9 (47.4) [0.274–0.680]
Second quartile (−12.0 to −3.0)	16	6 (37.5) [0.178–0.609]
Third quartile (−2.0 to −1.0)	16	9 (56.3) [0.333–0.773]
Fourth quartile (0.0 to 136.0)	27	14 (51.9) [0.347–0.687]

* The potential completer population includes all patients who were randomized more than 52 weeks prior to termination of the atacicept 150-mg arm. Values are the number (%) [90% confidence limit].
† The number of patients in the placebo-treated group in the IgG analysis was 81, and the number of patients in the placebo-treated group in both the naive B cell and plasma cell analyses was 41.

Relationship between treatment response and atacicept exposure. For the analysis of treatment response according to atacicept exposure, atacicept-treated patients were categorized into quartiles according to the average atacicept serum trough concentration over time. Flare rates were reduced in patients with higher levels of atacicept exposure (48.8% and 29.3% in the third and fourth quartiles, respectively) relative to those with lower levels of exposure (63.4% and 61.0% in the first and second quartiles, respectively) or those who received placebo (60.5%) (Table 2).

Safety. *Relationship between infection rate and biomarker levels.* There was no notable difference in the overall infection rate or the rate of serious or severe infection with atacicept compared with placebo in any of the 3 BLyS/APRIL subgroups (Table 3). Despite some small numerical differences, there was no correlation between the overall infection rate and reduced levels of IgG, IgM, or IgA or reduced naive B cell or plasma cell numbers (Table 4). Although higher rates of serious or severe infections were observed in patients with the greatest reductions in the IgM level compared with those with the lowest reduction (12.8% [n = 5] versus 0.0% [n = 0] for the first quartile compared with the fourth quartile), these data reflect small numbers of patients. No other trends toward an increased number of serious or severe infections were observed in any other biomarker quartiles.

Table 2. Rate of new disease flares in the placebo-treated and atacicept-treated patients in the potential completer population, according to atacicept exposure*

	No. of patients	New flare during treatment
Placebo	81	49 (60.5) [0.508–0.696]
Atacicept		
Average serum trough concentration, ng/ml		
First quartile (0.0 to 2,782.0)	41	26 (63.4) [0.494–0.759]
Second quartile (2,823.7 to 3,892.0)	41	25 (61.0) [0.469–0.738]
Third quartile (3,894.3 to 4,946.9)	41	20 (48.8) [0.351–0.626]
Fourth quartile (4,956.9 to 7,788.1)	41	12 (29.3) [0.178–0.431]

* The potential completer population includes all patients who were randomized more than 52 weeks prior to termination of the atacicept 150-mg arm. Values are the number (%) [90% confidence limit].

Table 3. Rate of infection in atacicept- and placebo-treated patients in the potential completer population, according to baseline levels of BLyS and APRIL*

	Placebo	Atacicept 75 mg	Atacicept 150 mg
Subgroup 1, high BlyS/high APRIL			
No. of patients	37	34	25
Any infection	21 (56.8) [0.420–0.707]	19 (55.9) [0.405–0.705]	13 (52.0) [0.341–0.695]
Serious/severe infection	3 (8.1) [0.022–0.196]	0 (0.0)	1 (4.0) [0.002–0.176]
Subgroup 2, high BlyS/low APRIL			
No. of patients	16	19	25
Any infection	10 (62.5) [0.391–0.822]	13 (68.4) [0.470–0.853]	17 (68.0) [0.496–0.830]
Serious/severe infection	0 (0.0)	1 (5.3) [0.003–0.226]	4 (16.0) [0.057–0.330]
Subgroup 3, low BlyS			
No. of patients	28	29	31
Any infection	14 (50.0) [0.333–0.667]	16 (55.2) [0.384–0.711]	18 (58.1) [0.418–0.731]
Serious/severe infection	0 (0.0)	3 (10.3) [0.029–0.246]	3 (9.7) [0.027–0.232]

* The potential completer population includes all patients who were randomized more than 52 weeks prior to termination of the atacicept 150-mg arm. The cutoff for high versus low BLyS levels was defined as ≥1.6 ng/ml. The cutoff for high versus low APRIL levels was defined as ≥2.2 ng/ml. Values are the number (%) of patients [90% confidence limit].

Neither of the 2 patients who died while receiving atacicept had an IgG level of <14.6 gm/liter (normal 7.0–16.0), and their lowest post-baseline values, representing a 19.0% and a 40.0% decrease from baseline, respectively, were still within normal levels (data not shown). Their IgM levels remained >0.34 gm/liter (normal 0.4–2.3), and their

Table 4. Rate of infection in atacicept- and placebo-treated patients in the potential completer population, according to change in IgG, IgA, IgM, naive B cell, and plasma cell levels from baseline to week 52, and atacicept exposure*

	No. of patients	Any infection during treatment	Serious/severe infection during treatment
Placebo	81	45 (55.6) [0.458–0.650]	3 (3.7) [0.010–0.093]
Atacicept			
Change in IgG, gm/liter			
First quartile (−15.4 to −6.3)	39	23 (59.0) [0.446–0.723]	4 (10.3) [0.036–0.220]
Second quartile (−6.2 to −4.0)	40	27 (67.5) [0.534–0.796]	3 (7.5) [0.021–0.183]
Third quartile (−3.9 to −2.9)	40	24 (60.0) [0.458–0.731]	2 (5.0) [0.009–0.149]
Fourth quartile (−2.8 to 2.0)	40	22 (55.0) [0.409–0.685]	3 (7.5) [0.021–0.183]
Change in IgM, gm/liter			
First quartile (−4.4 to −1.0)	39	24 (61.5) [0.471–0.746]	5 (12.8) [0.052–0.251]
Second quartile (−0.9 to −0.7)	39	25 (64.1) [0.497–0.768]	5 (12.8) [0.052–0.251]
Third quartile (−0.6 to −0.4)	39	22 (56.4) [0.421–0.700]	2 (5.1) [0.009–0.153]
Fourth quartile (−0.3 to 0.7)	42	25 (59.5) [0.457–0.723]	0 (0)
Change in IgA, gm/liter			
First quartile (−5.0 to −1.9)	39	22 (56.4) [0.421–0.700]	4 (10.3) [0.036–0.220]
Second quartile (−1.8 to −1.4)	40	26 (65.0) [0.508–0.774]	3 (7.5) [0.021–0.183]
Third quartile (−1.3 to −0.9)	40	27 (67.5) [0.534–0.796]	4 (10.0) [0.035–0.214]
Fourth quartile (−0.9 to 0.3)	40	21 (52.5) [0.385–0.662]	1 (2.5) [0.001–0.113]
Change in naive B cells/μl			
First quartile (−725.0 to −125.0)	19	10 (52.6) [0.320–0.726]	1 (5.3) [0.003–0.226]
Second quartile (−123.0 to −44.0)	20	14 (70.0) [0.492–0.860]	2 (10.0) [0.018–0.283]
Third quartile (−41.0 to −12.0)	18	12 (66.7) [0.446–0.844]	2 (11.1) [0.020–0.310]
Fourth quartile (−11.0 to 39.0)	21	15 (71.4) [0.513–0.868]	1 (4.8) [0.002–0.207]
Change in plasma cells/μl			
First quartile (−107.0 to −13.0)	19	10 (52.6) [0.320–0.726]	2 (10.5) [0.019–0.296]
Second quartile (−12.0 to −3.0)	16	13 (81.3) [0.583–0.947]	2 (12.5) [0.023–0.344]
Third quartile (−2.0 to −1.0)	16	12 (75.0) [0.516–0.910]	1 (6.3) [0.003–0.264]
Fourth quartile (0.0 to 136.0)	27	16 (59.3) [0.417–0.752]	1 (3.7) [0.002–0.164]
Average serum concentration, ng/ml			
First quartile (0.0 to 2,782.0)	41	27 (65.9) [0.519–0.780]	3 (7.3) [0.020–0.178]
Second quartile (2,823.7 to 3,892.0)	41	27 (65.9) [0.519–0.780]	7 (17.1) [0.083–0.297]
Third quartile (3,894.3 to 4,946.9)	41	23 (56.1) [0.421–0.694]	0 (0)
Fourth quartile (4,956.9 to 7,788.1)	41	20 (48.8) [0.351–0.626]	2 (4.9) [0.009–0.146]

* The potential completer population includes all patients who were randomized more than 52 weeks prior to termination of the atacicept 150-mg arm. Values are the number (%) [90% confidence limit].

lowest post-baseline values represented a 55.0% and a 77.0% decrease, respectively, from baseline (data not shown).

Relationship between infection rate and atacicept exposure. In the atacicept exposure analysis, there was no difference in the overall infection rate between any of the atacicept quartiles. Patients in the second quartile appeared to have higher rates of serious or severe infection (17.1%; n = 7) compared with placebo (3.7%; n = 3), but this result is difficult to interpret due to small patient numbers. Patients with the highest atacicept exposure levels had rates of serious or severe infections similar to those in the placebo group (3.7% in the placebo group and 4.9% in the atacicept fourth quartile).

The 2 patients who died due to infection had relatively low mean and maximum trough levels of atacicept. Patient A, who died of pneumococcal pneumonia and alveolar hemorrhage, received atacicept 150 mg and had a mean atacicept concentration of 1,759 ng/ml in the fifth percentile and a maximum concentration of 3,511 ng/ml in the seventh percentile. Patient B, who died of acute respiratory failure due to alveolar hemorrhage secondary to possible leptospirosis, had a mean concentration of 3,096 ng/ml in the 39th percentile and a maximum concentration of 4,303 ng/ml in the 29th percentile (results not shown).

DISCUSSION

It is well established that both BLyS and APRIL have roles in the pathogenesis of B cell–mediated autoimmunity, with elevated serum levels correlating with disease severity in patients with SLE (15,19,20,23,24). The results of this post hoc analysis of the APRIL-SLE study are largely consistent with this evidence. In the group treated with placebo, patients with the highest baseline serum levels of both BLyS and APRIL (subgroup 1) had the highest flare rates (75.7%), whereas patients with the lowest levels of baseline BLyS (subgroup 3) had the lowest flare rates (39.3%).

Another study showed that BLyS levels of ≥2.0 ng/ml at screening are an independent prognostic factor for an increased risk of BILAG A or B flares (25). Although the data reported here support this finding, BLyS and APRIL levels in this trial were measured at baseline after a 12-week steroid taper, as per the study design. It is likely that steroid treatment led to some decrease in the levels of BLyS and/or APRIL between screening and the time of baseline measurement. Indeed, improved disease activity was a prerequisite for randomization into the study.

In the placebo group, the observed increase in the flare rate between subgroup 2, in which only the BLyS level was high, and subgroup 1, in which both the BLyS and APRIL levels were high, suggests that APRIL levels may also have a contributory role in flares, at least in patients with high BlyS levels. In subgroup 3, which consisted of patients with low BLyS levels at baseline, APRIL levels had no effect on flare rates in the placebo group. Although this suggests that APRIL alone may not be prognostic for an increased risk of disease flare, it is difficult to speculate what effect APRIL levels had on flare in patients with low BLyS levels, due to the small sample sizes in subgroup 3.

A treatment response with atacicept was observed in the 2 patient subgroups with high baseline BLyS levels. In subgroup 1, a clear dose-dependent reduction in the flare rate was observed, and time to new flare was delayed in those treated with atacicept. The mechanism of action of atacicept should be considered when interpreting these results. A greater treatment effect size might be expected in patients with higher levels of the atacicept target molecules BLyS and APRIL. Indeed, the observation that the treatment response was more pronounced in subgroup 1, in which levels of both BLyS and APRIL were high, compared with subgroup 2, in which only BLyS levels were high, supports the hypothesis that elevated levels of both target molecules were required to achieve the maximum treatment response. This observation also raised the intriguing possibility that atacicept may be targeting heterotrimeric forms of BLyS/APRIL. Although both cytokines exist separately as homotrimers, heterotrimeric complexes containing both BLyS and APRIL also exist and are elevated in patients with autoimmune diseases (19). It is plausible, therefore, that by targeting each of these complexes, atacicept provides more complete inhibition of BlyS- and APRIL-mediated B cell activation and thus improved efficacy.

No response to treatment was observed in the patient population with low BlyS levels; however, because the flare rates were already low in this subgroup (as seen in those patients receiving placebo), a pronounced treatment effect was not expected. Interestingly, the treatment response in patients with low BLyS levels appeared not to be influenced by APRIL levels, even though the difference in the flare rate between subgroups 1 and 2 suggests that APRIL levels are important. Thus, BLyS levels above a minimum threshold level (e.g., ≥1.6 ng/ml in this trial) may be a prerequisite for a treatment response, although the reasons for this remain unclear.

A correlation was observed between reduced IgG levels and atacicept treatment. Notably, however,

IgG levels in each study arm were comparable regardless of BLyS/APRIL levels, suggesting that the correlation between BLyS/APRIL levels and treatment response was not influenced by any variations in IgG reductions.

We previously reported that levels of IgG, IgA, and IgM as well as B cell and plasma cell numbers were reduced in patients receiving atacicept compared with those receiving placebo in the APRIL-SLE study (21). Levels of anti-dsDNA antibodies were also reduced with atacicept treatment compared with placebo treatment in anti-dsDNA antibody–positive patients in the potential completer population in the APRIL-SLE study (21). This post hoc analysis suggests that greater decreases in IgG, IgA, and IgM levels and naive B cell and plasma cell numbers correlated with a greater treatment response. Although the link between reduced Ig levels and B cell counts and a reduced flare rate needs to be further established, it is possible that this may be attributable to a decreased production of pathogenic autoantibodies and/or reduced pathogenic B cell activity (e.g., cytokine production, antigen presentation to autoreactive T cells). Because only a subset of patients (n = 119) consented to the flow cytometric analysis, the observations on cell number reductions should be interpreted with caution.

There appeared to be an association between increased levels of atacicept exposure and reduced flare rates compared with placebo. Assuming that exposure levels are linked to the atacicept dose, this finding may account for the dose dependency seen in subgroups 1 and 2 in the BLyS/APRIL analysis. This would be consistent with the initial results of the APRIL-SLE study, which suggested that the higher atacicept dose, but not the lower dose, was associated with significantly reduced disease flare rates compared with placebo (21). The patient who died of pneumococcal pneumonia and alveolar hemorrhage (patient A) had mean and maximum concentrations of atacicept that fell within the fifth and seventh percentiles for the 150-mg dose, respectively. For context, the mean concentration of atacicept in the 75-mg group fell in the 10th percentile, and the maximum concentration was in the 25th percentile. Patient A, therefore, had relatively low atacicept exposure, despite receiving the higher dose. Taken together, these findings imply that using the higher 150-mg dose of atacicept may be more effective at controlling SLE disease activity than the lower 75-mg dose.

No statistically significant increased risk of infection with atacicept was observed in the APRIL-SLE study; however, infections were the most commonly reported serious adverse event (21). In this post hoc analysis, no clinically meaningful differences in the rates of overall or serious/severe infections were observed in any of the patient groups. In the atacicept exposure analysis, patients in the second quartile appeared to have higher infection rates compared with placebo; however, these values translated to a very small difference in actual patient numbers (n = 3 and n = 7 with placebo and atacicept, respectively) and could be a chance finding. Infection rates were not increased with atacicept compared with placebo even in those patients with the most pronounced reductions in IgG or IgA levels or naive B cell or plasma cell numbers. Higher rates of serious or severe infections were observed in patients with the greatest IgM level reduction compared with those with the least reduction, but these patient numbers were also too small to enable solid conclusions to be drawn. As reported previously (21), both patients who died due to fatal infections had IgG levels within the normal range, IgM levels just below the normal range, and atacicept concentrations within the lower end of that in the 150-mg treatment group. These results imply that neither the magnitude of pharmacodynamic effects nor the exposure levels of atacicept are strongly associated with infection rates. Infections are the most common cause of death in lupus patients (26), and patients should receive appropriate vaccinations regardless of whether they are receiving biologic agents (27).

In conclusion, this post hoc analysis shows that the response to atacicept was greatest in patients with high levels of both BLyS and APRIL, suggesting a potential predictive role for these target molecules. A potential stronger pharmacodynamic effect, as measured by Ig levels and B cell and plasma cell counts, appeared to be associated with a greater treatment response. It will be interesting to determine in future studies whether there is a potential for these markers to predict the likelihood of a clinical response. Importantly, increased atacicept exposure led to a more pronounced reduction in the flare rate. In addition, we could not detect an increased risk of infections associated with any subgroup, although the strength of this observation is limited by the small number of patients involved. These observations warrant the continued exploration of the higher dose of atacicept in addition to the lower dose in the ongoing phase IIb study, Efficacy and Safety of Atacicept in Systemic Lupus Erythematosus (ADDRESS II). These findings, however, provide further support for the primary findings of the APRIL-SLE study, indicating that atacicept has an acceptable risk–benefit profile in patients with SLE and is worthy of further study.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gordon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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